Testosterone Decanoate *(BANM, rINNM)* ⊗

Decanoato de testosterona; Testosteron Dekanoat; Testostérone, décanoate de; Testosteroni decanoas. 3-Oxoandrost-4-en-17β-yl decanoate; 17β-Hydroxyandrost-4-en-3-one decanoate.

Тестостерона Деканоат

$C_{29}H_{46}O_3$ = 442.7.
CAS — 5721-91-5.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Testosterone Decanoate). A white or almost white powder. Practically insoluble in water; very soluble in anhydrous alcohol, in acetone, and in dichloromethane; freely soluble in fatty oils. Store at a temperature of 2° to 8°.

Testosterone Enantate *(BANM, rINNM)* ⊗

Enantato de testosterona; NSC-17591; Testosteron enantát; Testostérone, enantate de; Testosterone Enanthate; Testosterone Heptanoate; Testosterone Heptylate; Testosteronenantat; Testosteroni enantas; Testosteronienantaatti; Testosterono enantatas; Testosteronu enantan; Tesztoszteronönantát. 3-Oxoandrost-4-en-17β-yl heptanoate; 17β-Hydroxyandrost-4-en-3-one heptanoate.

Тестостерона Энантат

$C_{26}H_{40}O_3$ = 400.6.
CAS — 315-37-7.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Testosterone Enantate). A white or yellowish-white crystalline powder. Practically insoluble in water; very soluble in dehydrated alcohol; freely soluble in fatty oils. Store at a temperature of 2° to 8°. Protect from light.
USP 31 (Testosterone Enanthate). A white or creamy-white crystalline powder. It is odourless or has a faint odour characteristic of heptanoic acid. Insoluble in water; very soluble in ether; soluble in vegetable oils. Store in a cool place.

Testosterone Isocaproate *(BANM, rINNM)* ⊗

Isocaproato de testosterona; Testosteron Isokaproat; Testostérone, isocaproate de; Testosterone Isohexanoate; Testosteroni isocaproas. 3-Oxoandrost-4-en-17β-yl 4-methylpentanoate; 17β-Hydroxyandrost-4-en-3-one 4-methylpentanoate.

Тестостерона Изокапронат

$C_{25}H_{38}O_3$ = 386.6.
CAS — 15262-86-9.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Testosterone Isocaproate). A white or almost white powder. Practically insoluble in water; very soluble in acetone and in dichloromethane; freely soluble in fatty oils.

Testosterone Phenylpropionate *(BANM, rINNM)* ⊗

Fenilpropionato de testosterona; Testosteron Fenilpropiyonat; Téstosterone, Phénylpropionate de; Testosteroni Phenylpropionas. 3-Oxoandrost-4-en-17β-yl 3-phenylpropionate; 17β-Hydroxyandrost-4-en-3-one 3-phenylpropionate.

Тестостерона Фенилпропионат

$C_{28}H_{36}O_3$ = 420.6.
CAS — 1255-49-8.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *BP(Vet)*.
BP(Vet) 2008 (Testosterone Phenylpropionate). A white to almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

Testosterone Propionate *(BANM, rINNM)* ⊗

NSC-9166; Propionato de testosterona; Testosteron Propiyonat; Testostérone, propionate de; Testosteroni propionas; Testosteronipropionaatti; Testosterono propionatas; Testosteronpropionat; Testosteron-propionát; Testosteronu propionian; Tesztoszteronpropionát. 3-Oxoandrost-4-en-17β-yl propionate; 17β-Hydroxyandrost-4-en-3-one propionate.

Тестостерона Пропионат

$C_{22}H_{32}O_3$ = 344.5.
CAS — 57-85-2.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Testosterone Propionate). A white or almost white powder or colourless crystals. Practically insoluble in water; freely soluble in alcohol and in acetone; soluble in fatty oils.
USP 31 (Testosterone Propionate). White or creamy-white, odourless, crystals or crystalline powder. Insoluble in water; freely soluble in alcohol, in dioxan, in ether, and in other organic solvents; soluble in vegetable oils. Protect from light.

Testosterone Undecylate *(rINNM)* ⊗

Org-538; Testosteron Undekanoat; Testosterone Undecanoate *(BANM, USAN)*; Testostérone, Undécylate de; Testosteroni Undecylas; Undecilato de testosterona. 3-Oxoandrost-4-en-17β-yl undecanoate; 17β-Hydroxyandrost-4-en-3-one undecanoate.

Тестостерона Ундесилат

$C_{30}H_{48}O_3$ = 456.7.
CAS — 5949-44-0.
ATC — G03BA03.
ATC Vet — QG03BA03.

Pharmacopoeias. In *Chin.*

Adverse Effects

Testosterone and other **androgens** may give rise to adverse effects related to their androgenic or anabolic activities. These include increased retention of sodium and water, oedema, hypercalcaemia, and impaired glucose tolerance. Other effects include increased low-density-lipoprotein cholesterol, decreased high-density-lipoprotein cholesterol, increased haematocrit, and suppression of clotting factors. Androgens may cause headache, depression, and gastrointestinal bleeding. It has been suggested that androgens may induce sleep apnoea in susceptible patients.

Abnormal liver function tests may occur and there have been reports of liver toxicity including jaundice and cholestatic hepatitis. There have also been reports of peliosis hepatis and hepatic tumours in patients who have received high doses over prolonged periods. These adverse hepatic effects have occurred primarily with the 17α-alkylated derivatives (e.g. methyltestosterone, stanozolol).

In men, large doses suppress spermatogenesis and cause testicular atrophy. Epididymitis and bladder irritability can occur. Priapism is a sign of excessive dosage and may occur especially in elderly males. Gynaecomastia may occur. Androgens may cause prostatic hyperplasia and accelerate the growth of malignant neoplasms of the prostate.

In women, the inhibitory action of androgens on the activity of the anterior pituitary results in the suppression of ovarian activity and menstruation. Continued use produces symptoms of virilism, such as hirsutism or male-pattern baldness, deepening of the voice, atrophy of the breasts and endometrial tissue, oily skin, acne, and hypertrophy of the clitoris. Virilisation may not be reversible, even after stopping therapy.

Large and repeated doses in early puberty may cause closure of the epiphyses and stop linear growth. Children may experience symptoms of virilisation: in boys there may be precocious sexual development with phallic enlargement and increased frequency of erection, and in girls, clitoral enlargement. Gynaecomastia may also occur in boys.

Masculinisation of the external genitalia of the female fetus may occur if androgens are given during pregnancy.

After transdermal application of testosterone, skin reactions may include irritation, erythema, allergic contact dermatitis, and sometimes burn-like lesions. Skin reactions are more common with patches that contain permeation enhancers.

The **anabolic steroids**, because they generally retain some androgenic activity, share the adverse effects of the androgens described above, but their virilising effects, especially in women, are usually less. There have been reports of adverse psychiatric effects in athletes taking large doses to try and improve performance. For adverse effects following the misuse of anabolic steroids, see Abuse under Precautions, below.

Carcinogenicity. Testosterone therapy is used in healthy older men with low or low-normal serum-testosterone concentrations (see Hypogonadism, under Uses and Administration, below), but there is some concern about a possible associated increase in prostate cancer risk. This concern is based on the fact that, regardless of any treatment, the incidence of prostate cancer increases with age, that normal prostate growth is dependent on androgens, and that androgen deprivation causes regression of advanced prostate cancer.[1] However, the relationship between androgens and the onset of prostate cancer is far from clear. Some data show that low serum-testosterone can predict more aggressive high-grade tumours, with a higher likelihood of metastatic disease and poorer outcome.[1,2] Although there have been reports of prostate cancer developing in men who have been treated with testosterone,[3] small clinical studies have, overall, not shown an increase in the risk of prostate cancer.[4] The effect of 6 months of testosterone enantate therapy on the prostate has been studied in 21 ageing men.[5] Although low serum-testosterone concentrations were normalised, there were no significant changes in androgen concentrations in prostate tissue, prostate volume, prostate specific antigen, or prostate cancer incidence. Further study of longer duration in larger numbers of men is needed to confirm the safety of this therapy.

In men with a history of prostate cancer, testosterone therapy for hypogonadism is generally contra-indicated because of the presumed risk of tumour recurrence. However, there are a small number of reports of testosterone being used safely after curative surgery, suggesting that testosterone therapy with close monitoring may be considered in such men with symptomatic hypogonadism.[6] There is even less data on the use of testosterone for hypogonadism in men who have been treated with radiotherapy with curative intent, or with androgen ablation by gonadorelin analogue therapy. Testosterone has also been used for hypogonadism in a small number of men with high-grade intra-epithelial neoplasia, a precancerous lesion, without increasing the risk of cancer development.[6]

For reference to hepatic malignancies associated with androgens and anabolic steroids, see Effects on the Liver, below. Renal cell carcinoma has also been reported after their abuse (see under Precautions, below).

1. Raynaud J-P. Prostate cancer risk in testosterone-treated men. *J Steroid Biochem Mol Biol* 2006; **102:** 261–6.
2. Barqawi A, Crawford ED. Testosterone replacement therapy and the risk of prostate cancer: is there a link? *Int J Impot Res* 2006; **18:** 323–8.
3. Brand TC, *et al*. Testosterone replacement therapy and prostate cancer: a word of caution. *Curr Urol Rep* 2007; **8:** 185–9.
4. Gould DC, Kirby RS. Testosterone replacement therapy for late onset hypogonadism: what is the risk of inducing prostate cancer? *Prostate Cancer Prostatic Dis* 2006; **9:** 14–18.
5. Marks LS, *et al.* Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006; **296:** 2351–61.
6. Kaufman J. A rational approach to androgen therapy for hypogonadal men with prostate cancer. *Int J Impot Res* 2006; **18:** 26–31.

Effects on the cardiovascular system. A cerebrovascular accident has been reported in a young man after the overzealous self-administration of testosterone enantate intramuscularly for hypogonadism.[1] It was noted that thromboembolic complications are not generally recognised as adverse effects of androgen therapy although there is some experimental evidence that testosterone stimulates thrombus formation. A systematic review[2] found evidence concerning cardiovascular events in studies of testosterone given to men with low or normal testosterone concentrations to be of poor quality, but some data to suggest that alterations in plasma lipid concentrations and blood pressure were not significant.

1. Nagelberg SB, *et al*. Cerebrovascular accident associated with testosterone therapy in a 21-year-old hypogonadal man. *N Engl J Med* 1986; **314:** 649–50.
2. Haddad RM, *et al*. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007; **82:** 29–39.

Effects on the liver. Hepatotoxicity, including elevations in liver enzymes, hepatic cholestasis and jaundice, and rarely peliosis hepatis and hepatic tumours, has occurred with androgens and anabolic steroids, particularly the 17α-alkylated derivatives. Prolonged treatment and high doses may be significant contributory factors. Tumours have included hepatocellular carcinomas, benign adenomas, and less commonly angiosarcomas and cholangiocarcinomas. Tumours and peliosis may regress on stopping therapy, but they can also progress to liver failure and death. Some reviews of the hepatic effects of androgens and anabolic steroids are cited below.[1-5] There has been a specific report of benign hepatic adenoma in a patient treated with testosterone enantate for 11 years,[6] and of hepatocellular carcinoma in a patient given testosterone enantate and methyltestosterone.[7] Further specific references may be found under individual drug monographs.

1. Bagheri SA, Boyer JL. Peliosis hepatis associated with androgenic-anabolic steroid therapy. *Ann Intern Med* 1974; **81:** 610–18.
2. Ishak KG, Zimmerman HJ. Hepatotoxic effects of the anabolic/androgenic steroids. *Semin Liver Dis* 1987; **7:** 230–6.
3. Søe KL, *et al*. Liver pathology associated with the use of anabolic-androgenic steroids. *Liver* 1992; **12:** 73–9.
4. Touraine RL, *et al*. Hepatic tumours during androgen therapy in Fanconi anaemia. *Eur J Pediatr* 1993; **152:** 691–3.
5. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *Am J Hematol* 2004; **77:** 257–67.
6. Carrasco D, *et al*. Hepatic adenomata and androgen treatment. *Ann Intern Med* 1984; **100:** 316.
7. Johnson FL. *et al.* Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* 1972; **ii:** 1273–6.

Effects on sexual function. Priapism has occurred after the use of testosterone for the management of delayed puberty[1-4] or hypogonadism.[5-7]

1. Zelissen PMJ, Stricker BHC. Severe priapism as a complication of testosterone substitution therapy. *Am J Med* 1988; **85:** 273–4.
2. Ruch W, Jenny P. Priapism following testosterone administration for delayed male puberty. *Am J Med* 1989; **86:** 256.
3. Madrid Garcia FJ, *et al.* Priapismo secundario a la administración de testosterona en el tratamiento del retraso puberal. *Arch Esp Urol* 2001; **54:** 703–5.
4. Arrigo T, *et al.* High-flow priapism in testosterone-treated boys with constitutional delay of growth and puberty may occur even when very low doses are used. *J Endocrinol Invest* 2005; **28:** 390–1.
5. Zargooshi J. Priapism as a complication of high dose testosterone therapy in a man with hypogonadism. *J Urol (Baltimore)* 2000; **163:** 907.
6. Shergill IS, *et al.* Testosterone induced priapism in Kallmann's syndrome. *J Urol (Baltimore)* 2003; **169:** 1089.
7. Ichioka K, *et al.* Testosterone-induced priapism in Klinefelter syndrome. *Urology* 2006; **67:** e17–e18.

Precautions

Testosterone and other androgens and anabolic steroids should be used cautiously in patients with cardiovascular disorders, renal or hepatic impairment, epilepsy, migraine, diabetes mellitus or other conditions that may be aggravated by the possible fluid retention or oedema caused. They should not be given to patients with hypercalcaemia or hypercalciuria, and should be used cautiously in conditions in which there is a risk of these developing such as skeletal metastases. The use of the 17α-alkylated derivatives, which are associated with an increased risk of hepatotoxicity, is probably best avoided in patients with hepatic impairment, and certainly if this is severe. Hepatic function should be monitored during therapy.

In men, androgens and anabolic steroids should not be given to those with carcinoma of the breast or prostate (although in women they have been used in the treatment of certain breast carcinomas; see also Carcinogenicity, above, regarding the use of testosterone in men with a history of prostate cancer). The prostate should be examined regularly during treatment.

Androgens and anabolic steroids should not be given during pregnancy because of the risk of virilisation of the female fetus.

Androgens and anabolic steroids should be used with extreme care in children because of the masculinising effects and also because premature closure of the epiphyses may occur resulting in inhibited linear growth and small stature. Skeletal maturation should be monitored during therapy.

Androgens and anabolic steroids may interfere with a number of clinical laboratory tests such as those for glucose tolerance and thyroid function.

Abuse. The adverse effects arising from the illicit use of androgens and anabolic steroids by athletes, often taken together at doses well in excess of those used therapeutically, have been discussed.[1-4] Such misuse is associated with potentially serious health risks. Effects have included abnormal liver function and hepatic neoplasms (see also Effects on the Liver, above), an atherogenic blood lipid profile and increased risk of cardiovascular disease, and reduced glucose tolerance. Hypogonadal states are commonly induced (azoospermia or oligospermia and testicular atrophy in men, and amenorrhoea or oligomenorrhoea in women). Gynaecomastia is relatively common in men, and virilisation in women. Psychiatric disturbances such as mania, hypomania, depression, aggression, and emotional lability, have been described. There is also some evidence that dependence associated with an acute withdrawal syndrome can occur. Rare reports include alterations in immune response, tendon damage, renal cell carcinoma, and peliosis hepatis.

There has been some dispute about the methods used to detect abuse of certain anabolic steroids in athletes. A study in healthy subjects has apparently confirmed endogenous production of small amounts of nandrolone metabolites;[5] a number of different factors might have an influence including genetics, intense exercise, trauma, and hypoglycaemic stress.[6]

1. Pärssinen M, Seppälä T. Steroid use and long-term health risks in former athletes. *Sports Med* 2002; **32:** 83–94.
2. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med* 2004; **34:** 513–54.
3. Maravelias C, *et al.* Adverse effects of anabolic steroids in athletes: a constant threat. *Toxicol Lett* 2005; **158:** 167–75.
4. Trenton AJ, Currier GW. Behavioural manifestations of anabolic steroid use. *CNS Drugs* 2005; **19:** 571–95.
5. Reznik Y, *et al.* Urinary nandrolone metabolites of endogenous origin in man: a confirmation by output regulation under human chorionic gonadotropin stimulation. *J Clin Endocrinol Metab* 2001; **86:** 146–50.
6. Kohler RMN, Lambert MI. Urine nandrolone metabolites: false positive doping test? *Br J Sports Med* 2002; **36:** 325–9.

Breast feeding. It is not known whether testosterone is distributed into breast milk, but it should be avoided in women who are breast feeding because of the theoretical potential androgenic effect on the infant. High doses of testosterone can suppress lactation.

Porphyria. Androgens are considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

A female patient with acute intermittent porphyria (p.1448) who suffered from severe attacks pre-menstrually was successfully managed with subcutaneous implants of testosterone when suppression of the menstrual cycle with buserelin met with limited success.[1]

1. Savage MW, *et al.* Acute intermittent porphyria treated by testosterone implant. *Postgrad Med J* 1992; **68:** 479–81.

Pregnancy. Reports of female fetal virilisation after maternal use of testosterone[1] or methyltestosterone[2] during pregnancy.

1. Reschini E, *et al.* Female pseudohermaphroditism due to maternal androgen administration: 25-year follow-up. *Lancet* 1985; **i:** 1226.
2. Dewhurst J, Gordon RR. Fertility following change of sex. *Lancet* 1984; **ii:** 1461.

Veterinary use. An FAO/WHO expert committee examining the risks from residue of veterinary drugs in foodstuffs established an acceptable daily intake for testosterone, but concluded that there would be no need to specify a numerical maximum residue limit for testosterone in the edible tissues of cattle when products are used as growth promotors according to good practice.[1] However, it should be noted that, in the EU, the use of androgens in veterinary practice is restricted and their use as growth promotors is banned. In addition, the use of anabolic steroids is banned in animals intended for human consumption.

1. FAO/WHO. Evaluation of certain veterinary drug residues in food: fifty-second report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 893* 2000. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_893.pdf (accessed 09/07/08)

Interactions

Testosterone and other androgens and anabolic steroids have been reported to enhance the activity of a number of drugs, with resulting increases in toxicity. Drugs affected include ciclosporin (see p.1828), levothyroxine (see p.2173), and anticoagulants such as warfarin (see p.1431). Resistance to the effects of neuromuscular blockers (p.1905) has also been reported. As androgens and anabolic steroids can alter glucose metabolism, doses of insulin or oral antidiabetics may need adjustment.

Pharmacokinetics

Testosterone is absorbed from the gastrointestinal tract, the skin, and the oral mucosa. However, testosterone undergoes extensive first-pass hepatic metabolism when given orally and is therefore usually given intramuscularly, subcutaneously, or transdermally. In addition, the basic molecule of testosterone has been modified to produce orally active compounds and to extend the duration of action. Alkylation of the 17α position produces compounds that are more slowly metabolised by the liver, and hence may be administered orally. Esterification of the 17β hydroxyl group increases lipid solubility and results in slower systemic absorption following intramuscular injection. The rate of absorption of the esters is related to the size of the ester group. The undecylate ester undergoes less complete inactivation after oral doses because of distribution into the lymphatic system. Testosterone esters are hydrolysed to testosterone after absorption.

Testosterone is about 80% bound to sex-hormone binding globulin. Derivatives of 19-nortestosterone and 17-α-methylated compounds have reduced binding to this globulin. The plasma half-life of testosterone is reported to range from about 10 to 100 minutes. It is largely metabolised in the liver via oxidation at the 17-OH group with the formation of androstenedione, which is further metabolised to the weakly androgenic androsterone and inactive etiocholanolone which are excreted in the urine mainly as glucuronides and sulfates. About 6% is excreted unchanged in the faeces after undergoing enterohepatic recirculation. Testosterone is converted to the more active dihydrotestosterone in some target organs by 5α-reductase. 19-Nortestosterone derivatives appear to be less susceptible to this enzyme. Small amounts of testosterone are aromatised to form oestrogenic derivatives, particularly oestradiol. Compounds with a saturated A-ring, such as mesterolone, appear to be less likely to be aromatised to oestrogen.

◊ References to the pharmacokinetics of subcutaneous testosterone pellets,[1] scrotal[2,3] and non-scrotal[4-7] transdermal patches, gel,[8,9] and a buccal preparation,[10,11] are given below.

1. Handelsman DJ, *et al.* Pharmacokinetics and pharmacodynamics of testosterone pellets in man. *J Clin Endocrinol Metab* 1990; **71:** 216–22.
2. Findlay JC, *et al.* Transdermal delivery of testosterone. *J Clin Endocrinol Metab* 1987; **64:** 266–8.
3. Cunningham GR, *et al.* Testosterone replacement with transdermal therapeutic systems: physiological serum testosterone and elevated dihydrotestosterone levels. *JAMA* 1989; **261:** 2525–30.
4. Meikle AW, *et al.* Pharmacokinetics and metabolism of a permeation-enhanced testosterone transdermal system in hypogonadal men: influence of application site. *J Clin Endocrinol Metab* 1996; **81:** 1832–40.
5. Yu Z, *et al.* Transdermal testosterone administration in hypogonadal men: comparison of pharmacokinetics at different sites of application and at the first and fifth days of application. *J Clin Pharmacol* 1997; **37:** 1129–38.
6. Dobs AS, *et al.* Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab* 1999; **84:** 3469–78.
7. Singh AB, *et al.* Pharmacokinetics of a transdermal testosterone system in men with end stage renal disease receiving maintenance hemodialysis and healthy hypogonadal men. *J Clin Endocrinol Metab* 2001; **86:** 2437–45.
8. Swerdloff RS, *et al.* Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J Clin Endocrinol Metab* 2000; **85:** 4500–10.
9. Marbury T, *et al.* Evaluation of the pharmacokinetic profiles of the new testosterone topical gel formulation, Testim , compared to AndroGel . *Biopharm Drug Dispos* 2003; **24:** 115–20.
10. Korbonits M, *et al.* A comparison of a novel testosterone bioadhesive buccal system, Striant, with a testosterone adhesive patch in hypogonadal males. *J Clin Endocrinol Metab* 2004; **89:** 2039–43.
11. Wang C, *et al.* New testosterone buccal system (Striant) delivers physiological testosterone levels: pharmacokinetics study in hypogonadal men. *J Clin Endocrinol Metab* 2004; **89:** 3821–9.

Uses and Administration

The natural hormone testosterone and its derivatives have anabolic and androgenic properties (for further details, see p.2058).

The primary indication for androgens, such as testosterone or its esters, is as replacement therapy in **male hypogonadal disorders** (below) caused by either pituitary or testicular disorders or in hypogonadism following orchidectomy. Testosterone may be used as a subcutaneous implant in a dose of 100 to 600 mg; plasma concentrations of testosterone are usually maintained within the physiological range for 4 to 5 months with a dose of 600 mg. It may also be given by transdermal delivery systems. Patches are applied to the back, abdomen, thighs or upper arms to supply 2.5 to 7.5 mg daily. A scrotal patch containing 10 or 15 mg of testosterone and supplying about 4 or 6 mg of testosterone in 24 hours has been used, but is no longer widely available. Hydroalcoholic gels containing 1 or 2% testosterone are also used; they are applied daily to the shoulders and upper arms, abdomen, or thighs, depending on the preparation. About 10% of the applied dose is absorbed across the skin to provide a systemic dose of testosterone 5 to 10 mg. A sustained-release adhesive buccal system that contains testosterone 30 mg is applied twice daily; by this route the systemic dose is about 3 mg. Testosterone has also been given by intramuscular injection in a dose of up to 50 mg two or three times weekly, but testosterone esters are generally preferred by this route.

The testosterone esters are usually formulated as oily solutions for intramuscular use to give a prolonged duration of action. Doses that have been used for the various esters are:

- testosterone cipionate 50 to 400 mg every 2 to 4 weeks

- testosterone enantate 50 to 400 mg every 2 to 4 weeks, or an initial dose of 250 mg every 2 to 3 weeks followed by maintenance dosing every 3 to 6 weeks
- testosterone propionate up to 50 mg two or three times weekly
- testosterone undecylate 1 g every 10 to 14 weeks

The isocaproate, phenylpropionate, and propionate esters may be given as a combined intramuscular preparation, sometimes also containing testosterone decanoate. Testosterone hexahydrobenzoate, testosterone hexahydrobenzylcarbonate, and testosterone isobutyrate have also been used. The undecylate ester is also given orally in an initial dose of 120 to 160 mg daily, in 2 divided doses, for 2 to 3 weeks, followed by a maintenance dose of 40 to 120 mg daily. See below for some doses of testosterone used in children.

Androgens and anabolic steroids have sometimes been used with oestrogens in the management of certain menopausal disorders, but the use of androgens and anabolic steroids in women with osteoporosis is no longer advocated because their adverse effects essentially outweigh any benefit they may produce. In the UK menopausal women are sometimes given implants of testosterone in a dose of 50 to 100 mg every 4 to 8 months as an adjunct to menopausal HRT for symptoms such as decreased libido. In the USA, preparations containing an androgen and an oestrogen are available for the treatment of menopausal vasomotor symptoms; intramuscular doses of testosterone cipionate 50 mg with estradiol cipionate 2 mg have been given once every 4 weeks, with attempts to taper treatment at 3 to 6 month intervals. However, there are concerns about the use of these preparations and conflicting opinion as to their usefulness (see below). More recently a transdermal patch has become available for the treatment of hypoactive sexual desire disorder in women with surgically induced menopause (bilateral oophorectomy and hysterectomy) who are receiving oestrogen therapy. The patch is applied twice weekly and delivers a daily systemic dose of testosterone 300 micrograms; the initial response to therapy should be evaluated after 3 to 6 months and reassessed every 6 months. In postmenopausal women androgens, and sometimes anabolic steroids are occasionally used in the hormonal therapy of disseminated breast carcinoma but care should be taken to choose a compound with a lower masculinising effect; the short-acting synthetic compounds are usually preferred for such purposes. Testosterone enantate has been used in doses of 200 to 400 mg every 2 to 4 weeks by intramuscular injection.

Anabolic steroids, and sometimes androgens, have been used in the treatment of refractory anaemias characterised by deficient red cell production, such as aplastic anaemia. Anabolic steroids and synthetic androgens with an attenuated action (sometimes known as 'attenuated androgens') such as danazol are also used in the management of hereditary angioedema.

Topical androgens may be used in the treatment of lichen sclerosus.

Androgens and anabolic steroids have been used for their anabolic properties in various catabolic states.

Testosterone hemisuccinate is an ingredient of preparations that have been promoted for the management of cataracts.

◊ General reviews of androgens and anabolic steroids.

1. Hickson RC, *et al.* Adverse effects of anabolic steroids. *Med Toxicol Adverse Drug Exp* 1989; **4:** 254–71.
2. Bagatell CJ, Bremner WJ. Androgens in men—uses and abuses. *N Engl J Med* 1996; **334:** 707–14.
3. Conway AJ, *et al.* Use, misuse and abuse of androgens: the Endocrine Society of Australia consensus guidelines for androgen prescribing. *Med J Aust* 2000; **172:** 220–4. Correction. *ibid.*; 334. Also available at: http://www.mja.com.au/public/issues/172_05_060300/conway/conway.html (accessed 13/11/07)
4. Handelsman DJ. Testosterone: use, misuse and abuse. *Med J Aust* 2006; **185:** 436–9.

Administration in children. Testosterone is used in adolescent males with hypogonadism, and has been used in constitutionally delayed puberty (see below). It has also been used to reduce final height in boys with constitutional tall stature (see below).

For the induction and maintenance of **sexual maturation** in boys over 12 years of age, the *BNFC* includes doses of testosterone undecylate 40 mg orally on alternate days, increasing up to 120 mg daily according to response. Alternatively, testosterone enantate or propionate may be given by deep intramuscular injection in doses of 25 to 50 mg/m^2 every month, increasing every 6 to 12 months according to response. An injection containing a combination of testosterone esters (isocaproate 40 mg, phenylpropionate 40 mg, and propionate 20 mg) has also been given intramuscularly, once each month for 3 doses, for delayed puberty. For boys over 15 years, the adult dose of a transdermal patch may be used, and an implant may be suitable for maintenance in hypogonadal males over 16 years (see above for doses). However, great care is necessary when using androgens for such conditions as bone growth and final height may be inhibited by the early fusion of the epiphyses. Extemporaneously prepared testosterone cream has been applied topically in the management of microphallus (the alcohol in proprietary gels can cause irritation).

Growth hormone provocation testing may be used in the diagnosis of growth hormone deficiency in children with growth retardation (p.1798). However, the response can be blunted in prepubertal and peripubertal children, resulting in false negative results. Hormonal **pituitary priming** using testosterone has been tried in boys in order to increase responsiveness to the test,[1-3] although there appears to be no consensus on such use.[4] The *BNFC* includes a single intramuscular dose of a product containing a combination of testosterone esters (isocaproate 40 mg, phenylpropionate 40 mg, and propionate 20 mg), given 3 to 5 days before the test.

1. Loche S, *et al.* The growth hormone response to hexarelin in children: reproducibility and effect of sex steroids. *J Clin Endocrinol Metab* 1997; **82:** 861–4.
2. Coutant R, *et al.* Body composition, fasting leptin, and sex steroid administration determine GH sensitivity in peripubertal short children. *J Clin Endocrinol Metab* 2001; **86:** 5805–12.
3. Gönç EN, *et al.* Comparison of stimulated growth hormone levels in primed versus unprimed provocative tests: effect of various testosterone doses on growth hormone levels. *Horm Res* 2001; **56:** 32–7.
4. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85:** 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 22/08/08)

Anabolic effects. The androgens generally possess anabolic activity and were formerly used to increase weight in patients suffering from emaciation or debilitating diseases but effectiveness was doubtful. The anabolic steroids were developed in order to enhance the ability to build proteins and diminish the virilising and masculinising effects of the natural androgens, but all anabolics retain some androgenic activity. The anabolic steroids have again, like the androgens, been used in an attempt to produce weight gain in cachexia and wasting diseases (p.2115).

The anabolic steroids and androgens have been the subject of much misuse and abuse by athletes, sports persons, and body builders (see under Precautions, above) in an attempt to increase muscle mass and body-weight but such use cannot be justified.

References to the anabolic effects of testosterone.

1. Bhasin S, *et al.* The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 1996; **335:** 1–7.
2. Basaria S, *et al.* Anabolic-androgenic steroid therapy in the treatment of chronic diseases. *J Clin Endocrinol Metab* 2001; **86:** 5108–17.
3. Kong A, Edmonds P. Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis. *Lancet Infect Dis* 2002; **2:** 692–9.
4. Johns K, *et al.* Anabolic steroids for the treatment of weight loss in HIV-infected individuals. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 13/11/07).

Antineoplastic-induced infertility. For reference to the use of testosterone to preserve gonadal function during cyclophosphamide therapy, see Effects on Reproductive Potential, p.702.

Constitutionally delayed puberty. Testosterone enantate given by intramuscular injection every 1 to 2 months for periods ranging from 3 months to several years, produced beneficial effects in boys with constitutionally delayed puberty and growth;[1,2] growth rate increased, sexual and skeletal maturation were stimulated, and full height potential did not appear to be compromised. However, it has been pointed out that repeated intramuscular injections are painful and are disliked by adolescents;[3] oral testosterone undecylate or oxandrolone have been shown to be effective in the treatment of delayed puberty and growth in boys,[4,5] and may be preferred.[3] It should be noted that giving androgens to boys with constitutional delay of growth and puberty is controversial (see p.2079). For reference to the use of testosterone in boys with delayed puberty due to hypogonadism see below.

1. Donaldson MDC, Savage DCL. Testosterone therapy in boys with delayed puberty. *Arch Dis Child* 1987; **62:** 647–8.
2. Richman RA, Kirsch LR. Testosterone treatment in adolescent boys with constitutional delay in growth and development. *N Engl J Med* 1988; **319:** 1563–7.
3. Kelnar CJH. Treatment of the short, sexually immature adolescent boy. *Arch Dis Child* 1994; **71:** 285–7.
4. Albanese A, *et al.* Oral treatment for constitutional delay of growth and puberty in boys: a randomised trial of an anabolic steroid or testosterone undecanoate. *Arch Dis Child* 1994; **71:** 315–17.
5. Brown DC, *et al.* A double blind, placebo controlled study of the effects of low dose testosterone undecanoate on the growth of small for age, prepubertal boys. *Arch Dis Child* 1995; **73:** 131–5.

Constitutionally tall stature. Supraphysiological doses of androgens have been used to *reduce* final height in tall adolescent boys. Testosterone esters in monthly doses of up to 1000 mg by intramuscular injection have been used.[1] Preliminary evidence after a mean of 10 years follow-up suggests that there was no long-term effect on reproductive function.[2] For reference to the use of testosterone to *increase* growth rate, see Constitutionally Delayed Puberty, above.

1. Drop SLS, *et al.* Sex steroid treatment of constitutionally tall stature. *Endocr Rev* 1998; **19:** 540–58.
2. de Waal WJ, *et al.* Long term sequelae of sex steroid treatment in the management of constitutionally tall stature. *Arch Dis Child* 1995; **73:** 311–15.

Dementia. There has been some suggestion that age-related reduction in endogenous testosterone may have a role in cognitive decline in men (see Dementia, p.362). In a longitudinal study[1] of 574 men who were followed for about 19 years, a lower calculated concentration of free testosterone was found to be one of a number of risk factors associated with the development of Alzheimer's disease. A possible role for testosterone treatment has therefore been proposed and some preliminary studies have been undertaken. A small short-term study[2] of older men with Alzheimer's disease or mild cognitive impairment reported improvements in some measures of cognitive function in patients given intramuscular testosterone. In another study,[3] however, testosterone applied as a topical gel was reported to improve quality of life as scored by the caregivers of men with mild Alzheimer's disease, but to have no significant effect on quality of life in healthy elderly men or on cognitive function in either group.

1. Moffat SD, *et al.* Free testosterone and risk for Alzheimer disease in older men. *Neurology* 2004; **62:** 188–93.
2. Cherrier MM, *et al.* Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology* 2005; **64:** 2063–8.
3. Lu PH, *et al.* Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. *Arch Neurol* 2006; **63:** 177–85.

Erectile dysfunction. Although testosterone is known to enhance libido its physiological role in erection is still not fully understood. Studies have produced mixed results, but suggest that men with sexual or erectile dysfunction (p.2179) and low baseline concentrations of testosterone may derive some benefit from testosterone monotherapy;[1,2] the use of testosterone may also have some benefit in those who have responded poorly to phosphodiesterase type-5 inhibitors.[1,3] However, because of limited evidence and the potential for adverse effects, therapy should probably be limited to men with severe hypogonadism[1,2] (see also Hypogonadism, below).

For reference to the use of a cream containing testosterone, isosorbide dinitrate, and codergocrine mesilate in the treatment of erectile dysfunction, see under Glyceryl Trinitrate, p.1298.

1. Mikhail N. Does testosterone have a role in erectile function? *Am J Med* 2006; **119:** 373–82.
2. Boloña ER, *et al.* Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007; **82:** 20–8.
3. Shabsigh R, *et al.* The evolving role of testosterone in the treatment of erectile dysfunction. *Int J Clin Pract* 2006; **60:** 1087–92.

Gender reassignment. Testosterone is used in female-to-male transsexuals to develop and maintain secondary sexual characteristics.[1,2] A testosterone ester, or a combination of esters, is usually given by intramuscular injection in doses of 200 to 250 mg every 2 weeks, adjusted according to response.[2,3] Alternatively, testosterone undecylate 1 g may be given once every 10 to 12 weeks.[3] Oral or transdermal testosterone is less commonly used, and the addition of a progestogen may be needed to fully suppress menstruation in non-oophorectomised patients.[2]

1. Moore E, *et al.* Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. *J Clin Endocrinol Metab* 2003; **88:** 3467–73.
2. Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res* 2005; **64** (suppl 2): 31–6.
3. Gooren LJ, *et al.* Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 2008; **93:** 19–25.

Heart failure. Low serum-testosterone concentrations have been reported in men with chronic heart failure (p.1165). A study in men with moderate heart failure and low or low-normal testosterone concentrations found that 12 months of transdermal testosterone therapy improved symptoms of heart failure and exercise capacity.[1] The mechanism of benefit was unclear.

1. Malkin CJ, *et al.* Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J* 2006; **27:** 57–64.

Hypogonadism. Replacement therapy with testosterone or a testosterone ester is the standard treatment for *primary hypogonadism* in men (see p.2079). The androgen is often given as an intramuscular depot injection of one of the esters, although subcutaneous implants, oral formulations, transdermal systems, topical gel, and a buccal preparation are also used (for doses see

above).[1-3] Testosterone is also used to promote masculinisation in hypogonadal adolescent boys,[4,5] and is of value in the prevention of osteoporosis in hypogonadal men.[6,7] Testosterone has a negative feedback effect on gonadotrophin secretion, therefore any remaining spermatogenesis is generally suppressed; androgens are thus rarely useful in reversing male infertility (p.2080). Recommendations for monitoring therapy have been made.[3,8]

Transdermal testosterone may possibly be of benefit as an adjunct to oestrogen replacement in *women* who have undergone hysterectomy and oophorectomy (see Menopausal Hormone Replacement Therapy, below).

There has also been growing interest in the use of testosterone therapy in *healthy older men*, although there is limited evidence to prove a direct association between clinical changes and the natural decline of endogenous hormone concentrations with age.[9] This aspect of ageing is increasingly being described as the andropause, but the fall in testosterone concentrations is gradual, and not a rapid and significant decline of hormones with loss of fertility like that which occurs in the female menopause[9,10] (p.2071); other terms such as partial androgen deficiency or late-onset hypogonadism have also been proposed.[9] Testosterone therapy has been studied in healthy older men with normal or low-normal serum-testosterone concentrations. Modest beneficial changes in body composition (increased lean body-mass and decreased fat-mass) have been reported, but many studies have found no associated improvement in muscle strength, mobility, or functional autonomy, or a reduced risk of falls. Results are also inconsistent or negative from studies measuring skeletal effects, sexual function, cognitive function, mood, and quality of life.[9] A meta-analysis[11] of 8 studies suggested that intramuscular testosterone might be more effective than transdermal administration for increasing lumbar bone mineral density. There are concerns about potential adverse effects of testosterone on the prostate (see Carcinogenicity, above) and the cardiovascular system, and high doses have been reported to cause or exacerbate sleep apnoea.[9,12] Although recommendations have been made for the use and monitoring of testosterone therapy in healthy older men with androgen deficiency,[12-14] many caution that until further clinical studies have been done it should only be used in those with confirmed hypogonadism.[9,10]

1. Gooren LJG, Bunck MCM. Androgen replacement therapy: present and future. *Drugs* 2004; **64:** 1861–91.
2. Nieschlag E. Testosterone treatment comes of age: new options for hypogonadal men. *Clin Endocrinol (Oxf)* 2006; **65:** 275–81.
3. Bhasin S, *et al.* Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006; **91:** 1995–2010. Also available at: http://www.endo-society.org/guidelines/final/upload/AndrogensMenGuideline053006.pdf (accessed 22/08/08)
4. Moorthy B, *et al.* Depot testosterone in boys with anorchia or gonadotrophin deficiency: effect on growth rate and adult height. *Arch Dis Child* 1991; **66:** 197–9.
5. Zacharin MR, Warne GL. Treatment of hypogonadal adolescent boys with long acting subcutaneous testosterone pellets. *Arch Dis Child* 1997; **76:** 495–9.
6. Wang C, *et al.* Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. *Clin Endocrinol (Oxf)* 2001; **54:** 739–50.
7. Zacharin MR, *et al.* Bone mineral density outcomes following long-term treatment with subcutaneous testosterone pellet implants in male hypogonadism. *Clin Endocrinol (Oxf)* 2003; **58:** 691–5.
8. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004; **350:** 482–92.
9. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev* 2005; **26:** 833–76.
10. Juul A, Skakkebæk NE. Androgens and the ageing male. *Hum Reprod Update* 2002; **8:** 423–33.
11. Tracz MJ, *et al.* Testosterone use in men and its effects on bone health: a systematic review and meta-analysis of randomized placebo-controlled trials. *J Clin Endocrinol Metab* 2006; **91:** 2011–16.
12. Liu PY, *et al.* The rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. *J Clin Endocrinol Metab* 2004; **89:** 4789–96.
13. Nieschlag E, *et al.* Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, and EAU recommendations. *J Androl* 2006; **27:** 135–7. Also published in *Eur Urol* 2005; **48:** 1–4. and *Int J Androl* 2005; **28:** 125–7.
14. Wald M, *et al.* Testosterone replacement therapy for older men. *J Androl* 2006; **27:** 126–32.

Lichen sclerosus. Topical androgens such as androstanolone and testosterone have been used to treat vulvar lichen sclerosus (p.1580) in postmenopausal women.[1-4] However, virilisation can occur and a topical corticosteroid is generally preferred.[5]

1. Paslin D. Treatment of lichen sclerosus with topical dihydrotestosterone. *Obstet Gynecol* 1991; **78:** 1046–9.
2. Bracco GL, *et al.* Clinical and histologic effects of topical treatments of vulval lichen sclerosus: a critical evaluation. *J Reprod Med* 1993; **38:** 37–40.
3. Paslin D. Androgens in the topical treatment of lichen sclerosus. *Int J Dermatol* 1996; **35:** 298–301.
4. Joura EA, *et al.* Short-term effects of topical testosterone in vulvar lichen sclerosus. *Obstet Gynecol* 1997; **89:** 297–9.
5. Neill SM, *et al.* British Association of Dermatologists. Guidelines for the management of lichen sclerosus. *Br J Dermatol* 2002; **147:** 640–9. Also available at: http://www.bad.org.uk/healthcare/guidelines/Lichen_Sclerosus.pdf (accessed 13/11/07)

Male contraception. In male contraceptive studies it was found that high-dose testosterone severely reduced sperm production.[1] In those in whom azoospermia was not induced there was oligozoospermia with remaining sperm having a markedly reduced fertilising capacity. In a multicentre study carried out by WHO[2] involving 271 healthy fertile men, weekly intramuscular injection of testosterone enantate 200 mg produced azoospermia in 157 men within 6 months. In a subsequent 12-month study of these azoospermic men, during which time testosterone enantate was the only contraceptive measure used, there was only 1 pregnancy. Spermatogenesis was re-established on withdrawal of testosterone. These findings have been confirmed in a larger study of the same regimen, which additionally assessed contraceptive efficacy in men who achieved oligozoospermia (less than 3×10^6/mL).[3] No pregnancies occurred in couples where the man was azoospermic. However, the pregnancy rate was 8.1 per 100-person-years in the subgroup of couples where the man was oligozoospermic. This rate is sixfold higher than is generally seen with hormonal contraceptives in women.[4] Both studies found that consistent azoospermia was achieved in a higher percentage of Asian men (95%) than Western men (70%).[4] Testosterone undecylate has also been studied as a longer-acting intramuscular injection. In a study[5] involving Chinese men, a loading dose of 1000 mg followed by monthly maintenance doses of 500 mg effectively and persistently suppressed spermatogenesis in about 95% of 296 men who had initially responded; pregnancy occurred in the partner of 1 of the 6 men with sperm rebound.

An alternative approach being investigated is the use of testosterone with a progestogen, which enhances the suppression of spermatogenesis and may allow lower doses of androgen to be used with fewer adverse effects. Progestogens under investigation include cyproterone, desogestrel, etonogestrel, levonorgestrel, medroxyprogesterone, and norethisterone.[6,7]

For a general discussion on choice of contraceptive method, including mention of male contraception, see p.2070.

1. Matsumoto AM. Is high dosage testosterone an effective male contraceptive agent? *Fertil Steril* 1988; **50:** 324–8.
2. WHO Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. *Lancet* 1990; **336:** 955–9.
3. WHO Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. *Fertil Steril* 1996; **65:** 821–9.
4. Anonymous. An androgen contraceptive for men: preliminary findings. *WHO Drug Inf* 1996; **10:** 50–3.
5. Gu Y-Q, *et al.* A multicenter contraceptive efficacy study of injectable testosterone undecanoate in healthy Chinese men. *J Clin Endocrinol Metab* 2003; **88:** 562–8.
6. Amory JK, *et al.* Drug insight: Recent advances in male hormonal contraception. *Nat Clin Pract Endocrinol Metab* 2006; **2:** 32–41.
7. Grimes DA, *et al.* Steroid hormones for contraception in men. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 13/11/07).

Menopausal hormone replacement therapy. Menopause does not necessarily result in androgen deficiency in women, and androgen replacement is therefore not routinely required (see Menopausal Disorders, p.2077). In the UK menopausal women may nonetheless sometimes be given implants of testosterone as an adjunct to menopausal HRT. In the USA, injectable preparations containing an androgen and an oestrogen are available for the treatment of menopausal vasomotor symptoms, but there is conflicting opinion as to their usefulness, and further data are needed.[1] In Canada, a preparation containing estradiol and testosterone esters for intramuscular injection (*Climacteron; Sabex, Canad.*) was discontinued in 2005 because of concerns that testosterone is partially metabolised to oestrogen, which should be opposed by a progestogen in women with a uterus, and that there was no established dose of progestogen that could be recommended in this situation.[2] A study[3] in healthy postmenopausal women found that oral testosterone alone did not stimulate endometrial proliferation as estradiol did, and that it appeared to reduce the effect of estradiol when they were used together. However, therapy was given for only 3 months and long-term effects need further study. Improvements in mood and libido have been shown when androgens were given to postmenopausal women with an established cause of androgen deficiency such as surgically induced menopause.[4] A systematic review of the addition of testosterone to postmenopausal HRT considered that there was some evidence of benefit on sexual function, but that studies varied too much to estimate the effect of any particular combination.[5] More recently, a number of placebo-controlled studies in women with surgically induced[6-9] or natural[10] menopause have reported improvements in sexual activity and desire with transdermal testosterone. A product (*Intrinsa; Proctor and Gamble, UK*) has been licensed for use in the UK for the treatment of hypoactive sexual desire disorder in women with surgically induced menopause who are also receiving oestrogen replacement therapy, but the FDA has not licensed it in the USA and has expressed concern about the lack of data on long-term safety.[11] However, the North American Menopause Society[12] has recommended that testosterone therapy may be considered for postmenopausal women who present with symptoms of decreased sexual desire associated with personal distress and who have no other identifiable cause for their sexual concerns. Nevertheless, they warn that use of testosterone without estrogen cannot be recommended because there is no information on safety and efficacy in this situation, that topical preparations are preferred over oral products, that the lowest dose should be used for the shortest time, and that there is insufficient efficacy and safety data for therapy beyond 6 months.

The Endocrine Society[13] has evaluated data on the use of testosterone in various groups of women, including those with menopausal symptoms, and advises that although there is some evidence for efficacy in selected populations, such as surgically menopausal women, it cannot be recommended for generalised use because of poorly-defined indications and a lack of evidence on long-term safety.

The use of transdermal testosterone, with oestrogen and progestogen replacement therapy, is also being investigated in young women with spontaneous premature ovarian failure.[14]

1. Abraham D, Carpenter PC. Issues concerning androgen replacement therapy in postmenopausal women. *Mayo Clin Proc* 1997; **72:** 1051–5.
2. Sandoz Canada. Discontinuation of Climacteron Injection (estradiol dienanthate/estradiol benzoate and testosterone enanthate benzilic acid hydrazone injection in corn oil) (issued 23rd November, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/climacteron_hpc-cps-eng.pdf (accessed 22/08/08)
3. Zang H, *et al.* Effects of testosterone treatment on endometrial proliferation in postmenopausal women. *J Clin Endocrinol Metab* 2007; **92:** 2169–75.
4. Arlt W. Androgen therapy in women. *Eur J Endocrinol* 2006; **154:** 1–11.
5. Somboonporn W, *et al.* Testosterone for peri- and postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 13/11/07).
6. Shifren JL, *et al.* Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000; **343:** 682–8.
7. Simon J, *et al.* Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005; **90:** 5226–33.
8. Braunstein GD, *et al.* Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med* 2005; **165:** 1582–9.
9. Buster JE, *et al.* Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005; **105:** 944–52.
10. Shifren JL, *et al.* Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause* 2006; **13:** 770–9.
11. Moynihan R. FDA panel rejects testosterone patch for women on safety grounds. *BMJ* 2004; **329:** 1363.
12. North American Menopause Society. The role of testosterone therapy in postmenopausal women: position statement of The North American Menopause Society. *Menopause* 2005; **12:** 497–511. Also available at: http://www.menopause.org/aboutmeno/PStestosterone.pdf (accessed 13/11/07)
13. Wierman ME, *et al.* Androgen therapy in women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006; **91:** 3697–3710. Also available at: http://www.endo-society.org/guidelines/final/upload/Androgens_in_Women_CG.pdf (accessed 22/08/08)
14. Kalantaridou SN, *et al.* A pilot study of an investigational testosterone transdermal patch system in young women with spontaneous premature ovarian failure. *J Clin Endocrinol Metab* 2005; **90:** 6549–52.

Rheumatoid arthritis. A hypogonadal condition characterised by low serum-testosterone concentrations appears to be associated with at least the active stages of rheumatoid arthritis (p.11) in men.[1] Clinical improvement and reductions in IgM rheumatoid factor concentration, tender joint count, and the daily dosage of NSAIDs required, were observed in a small study[1] of men with rheumatoid arthritis and low serum-testosterone concentrations given oral testosterone undecylate 40 mg three times daily for 6 months. Improvements in rheumatoid arthritis were also seen in 12 of 36 postmenopausal women treated with intramuscular testosterone 50 mg plus a low dose of progesterone (2.5 mg) once every 2 weeks compared with 2 of 32 women receiving placebo.[2] However, a placebo-controlled study[3] in 30 men with normal serum-testosterone concentrations found no beneficial effect from intramuscular testosterone enantate on measures of disease activity.

1. Cutolo M, *et al.* Androgen replacement therapy in male patients with rheumatoid arthritis. *Arthritis Rheum* 1991; **34:** 1–5.
2. Booij A, *et al.* Androgens as adjuvant treatment in postmenopausal female patients with rheumatoid arthritis. *Ann Rheum Dis* 1996; **55:** 811–15.
3. Hall GM, *et al.* A randomized trial of testosterone therapy in males with rheumatoid arthritis. *Br J Rheumatol* 1996; **35:** 568–73.

Preparations

BP 2008: Testosterone Implants; Testosterone Propionate Injection;
USP 31: Testosterone Cypionate Injection; Testosterone Enanthate Injection; Testosterone Injectable Suspension; Testosterone Propionate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Androlone; Androtag; Nebido; Sustanon 250; Testoviron Depot 100; Testoviron Depot 250; Undestor; ***Austral.:*** Andriol; Androderm; Primoteston Depot; Reandron; Sustanon 100; Sustanon 250; Testogel; ***Austria:*** Andriol; Nebido; Reandron; Testoderm; Testoviron 250; ***Belg.:*** AndroGel; Sustanon 250; Testim; Testocaps; Undestor†; ***Braz.:*** Androxon; Deposteron; Nebido; ***Canad.:*** Andriol; Androderm; AndroGel; Delatestryl; ***Chile:*** Actiser-T; Nebido; Primoniat Depot; Sustenan; Sustenan 250; Testocaps; ***Cz.:*** Agovirin; AndroGel; Intrinsa; Livensa; Nebido; Sustanon; Testopatch; Tostran; Undestor; ***Denm.:*** Andriol; Nebido; Restandol; Testogel; Testoviron Depot 135; Testoviron Depot 250; ***Fin.:*** Atmos; Nebido; Panteston; Sustanon 250; Testim; Testogel; ***Fr.:*** AndroGel; Androtardyl; Intrinsa; Nebido; Pantestone; Testopatch; ***Ger.:*** Andriol; Androderm†; Androtop; Nebido; Striant; Testim; Testogel; Testoviron Depot 250; ***Gr.:*** Androderm; Andropatch; Nebido; Restandol; Testim; Testoviron; ***Hong Kong:*** Andriol; Sustanon; Testoviron Depot; ***Hung.:*** Andriol; Nebido; ***India:*** Aquaviron; Nuvir; Sustanon 100; Sustanon 250; Testanon 25; Testanon 50; Testoviron Depot; ***Indon.:*** Andriol Testocaps; Nebido; Sustanon 250; ***Irl.:*** Andropatch; Nebido; Restandol; Striant; Sustanon 100; Sustanon 250; Testim; Tes-

togel; ***Israel:*** AndroGel; Androxon; Sustanon 250; Testoviron Depot; ***Ital.:*** Andriol; Androderm†; AndroGel; Sustanon; Testim; Testo-Enant; Testogel; Testovis; ***Malaysia:*** Andriol; Jenasteron†; Nebido; ***Mex.:*** Andriol; Nebido; Primoteston Depot; Sostenon; Testoprim-D; ***Neth.:*** Andriol; AndroGel; Nebido; Striant; Sustanon 100; Sustanon 250; Testim; Testogel; Testoviron Depot†; ***Norw.:*** Andriol; Androxon†; Atmos; Nebido; Testogel; ***NZ:*** Androderm; Panteston; Primoteston Depot; Sustanon; ***Philipp.:*** Andriol; Nebido; ***Pol.:*** Nebido; Omnadren; Testosteronum Prolongatum; Undestor; ***Port.:*** Andriol; AndroGel; Intrinsa; Livensa; Nebido; Striant; Testim; Testogel; Testopatch; Testoviron Depot; Tostran; ***Rus.:*** Andriol (Андриол); AndroGel (Андрогель); Nebido (Небидо); Omnadren (Омнадрен); ***S.Afr.:*** Androxon; Depotrone; Sustanon 250; ***Singapore:*** Andriol; Sustanon 250; ***Spain:*** Androderm; Numanis; Reandron; Testex; Testim; Testogel; Testoviron Depot 250; ***Swed.:*** Atmos; Nebido; Testim; Testogel; Testoviron Depot; Tostrex; Undestor; ***Switz.:*** Andriol; Androderm; Nebido; Testoderm†; Testogel; Testoviron Depot; ***Thai.:*** Andriol; Testoviron 100†; Testoviron Depot; Virormone†; ***Turk.:*** Afro; Sustanon 250; Virigen; ***UK:*** Andropatch; Intrinsa; Nebido; Restandol; Striant; Sustanon 100; Sustanon 250; Testim; Testogel; Testosterone Implants; Tostran; Virormone; ***USA:*** Androderm; AndroGel; Delatestryl; Striant; Testim; Testoderm†; Testopel; Virilon†; ***Venez.:*** Andriol; AndroGel; Polysteron 250; Proviron Depot.

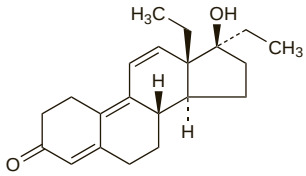
Multi-ingredient: ***Arg.:*** Supligol†; ***Braz.:*** Durateston; Estandron P; Trinestril; ***Canad.:*** Climacteron; ***Chile:*** Estandron Prolongado; ***Cz.:*** Folivirin; ***Ger.:*** Androfemon†; Testoviron Depot 100†; Testoviron Depot 50†; ***India:*** Mixogen; ***Ital.:*** Facovit; Testoviron; ***Malaysia:*** Sustanon 250; ***Mex.:*** Despamen; Sten; ***Neth.:*** Estandron Prolongatum; ***Norw.:*** Primoteston Depot; ***Port.:*** Sustenon 250; ***S.Afr.:*** Mixogen; Primodian Depot; ***Spain:*** Testoviron Depot 100; ***Thai.:*** Metharmon-F; Primodian Depot; ***Turk.:*** Estandron Prolongatum; ***USA:*** Depo-Testadiol; Depotestogen.

Tetrahydrogestrinone ⊗

THG. 18a-Homo-pregna-4,9,11-trien-17β-ol-3-one; .

$C_{21}H_{28}O_2$ = 312.4.

CAS — 618903-56-3.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of tetrahydrogestrinone: The Clear.

Profile

Tetrahydrogestrinone is a synthetic anabolic steroid that is structurally related to gestrinone (p.2106) and trenbolone (p.2135). It has been subject to abuse in sport.

Action. Tetrahydrogestrinone had androgenic and progestogenic activity in a yeast-based *in-vitro* bioassay study.[1] The anabolic and androgenic properties of tetrahydrogestrinone have also been studied in *animals*.[2-4]

1. Death AK, *et al.* Tetrahydrogestrinone is a potent androgen and progestin. *J Clin Endocrinol Metab* 2004; **89:** 2498–2500.
2. Labrie F, *et al.* Tetrahydrogestrinone induces a genomic signature typical of a potent anabolic steroid. *J Endocrinol* 2005; **184:** 427–33.
3. Jasuja R, *et al.* Tetrahydrogestrinone is an androgenic steroid that stimulates androgen receptor-mediated, myogenic differentiation in C3H10T1/2 multipotent mesenchymal cells and promotes muscle accretion in orchidectomized male rats. *Endocrinology* 2005; **146:** 4472–8.
4. Friedel A, *et al.* Tetrahydrogestrinone is a potent but unselective binding steroid and affects glucocorticoid signalling in the liver. *Toxicol Lett* 2006; **164:** 16–23.

Tibolone *(BAN, USAN, rINN)* ⊗

7α-Methylnorethynodrel; Org-OD-14; Tibolon; Tibolona; Tiboloni; Tibolonum. 17β-Hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one.

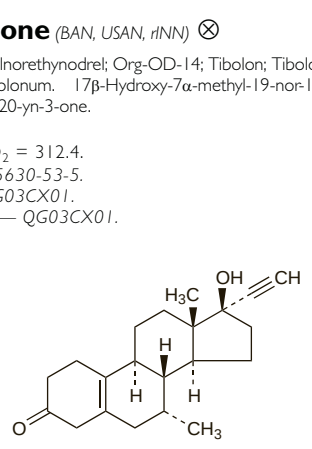
Тиболон

$C_{21}H_{28}O_2$ = 312.4.

CAS — 5630-53-5.

ATC — G03CX01.

ATC Vet — QG03CX01.



Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Tibolone). A white or almost white, crystalline powder or crystals. It exhibits polymorphism. Practically insoluble in water; soluble in acetone and in methyl alcohol. Store at a temperature of 2° to 8°.

Adverse Effects

Irregular vaginal bleeding or spotting may occur with tibolone, mainly during the first few months of treatment; unlike cyclical, but similar to continuous, combination HRT (p.2071), tibolone does not produce regular withdrawal bleeding. Other effects on the genital tract may include leucorrhoea, pruritus, candidiasis, and vaginitis. Other adverse effects have included breast pain, weight gain, oedema, dizziness, skin reactions, headache, migraine, visual disturbances, gastrointestinal disturbances, hypertrichosis, altered liver function, depression, and arthralgia or myalgia.

Incidence of adverse effects. In 1994, the UK CSM had received reports of 2796 suspected adverse reactions with tibolone over 3 years, out of about 666 000 prescriptions.[1] The commonest reported effects were headache, dizziness, nausea, rash, itching, and weight gain. Vaginal bleeding appeared to occur in about 8 to 9% of recipients. There had also been 52 reports of migraine, 4 of exacerbation of migraine, and 49 reports of visual disturbances, some suggestive of migraine.

1. CSM/MCA. Tibolone (Livial). *Current Problems* 1994; **20:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015632&RevisionSelectionMethod=LatestReleased (accessed 18/08/08)

Carcinogenicity. ***BREAST.*** The large cohort Million Women study[1] examined breast cancer incidence and mortality in relation to HRT use. After an average follow-up of 2.6 years for incidence, and 4.1 years for mortality, data were available for a group of 18 186 women who had used tibolone. There were 184 cases of invasive breast cancer equating to an overall risk of 1.45 (95% confidence interval 1.25 to 1.68) relative to women who had never used HRT. This was between the relative risks calculated for oestrogen-only HRT (1.30) and combined HRT (2.00). The risk was raised for current but not past use of tibolone, and increased with total duration of use.

For comment on the risk of recurrence in women with a history of breast cancer see Malignant Neoplasms under Precautions, below.

1. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; **362:** 419–27. Correction. *ibid.*; 1160.

ENDOMETRIUM. Endometrial hyperplasia and endometrial carcinoma have been rarely reported after investigation of uterine bleeding in women receiving tibolone therapy,[1-3] as has exacerbation of adenomyosis.[4] Some of these women had previously received oestrogens.

A cohort and nested case-control study[5] found that tibolone might have been associated with an increased risk of endometrial cancer compared with conventional forms of combined HRT, but the data were weak and might have been affected by bias and uncontrolled confounding factors. The large cohort Million Women Study[6] of HRT included a group of 28 028 who had used tibolone for an average of about 3 years. The risk of endometrial cancer was increased to 1.79 (95% confidence interval 1.43 to 2.25) in those who had used tibolone, compared with women who had never used HRT, and the risk was higher with more than 3 years of use compared with shorter durations. In contrast, a smaller randomised study[7] comparing tibolone with combined HRT recorded no cases of endometrial hyperplasia or carcinoma in 1317 women given tibolone for up to 2 years.

1. von Dadelszen P, *et al.* Endometrial hyperplasia and adenocarcinoma during tibolone (Livial) therapy. *Br J Obstet Gynaecol* 1994; **101:** 158–61.
2. Ginsburg J, Prelevic GM. Cause of vaginal bleeding in postmenopausal women taking tibolone. *Maturitas* 1996; **24:** 107–10.
3. Yazigi R, *et al.* Carcinoma of the endometrium in patients treated with tibolone. *Gynecol Oncol* 2004; **93:** 568–70.
4. Prys Davies A, Oram D. Exacerbation of adenomyosis in a postmenopausal woman taking tibolone associated with an elevation in serum CA 125. *Br J Obstet Gynaecol* 1994; **101:** 632–3.
5. de Vries CS, *et al.* Tibolone and endometrial cancer: a cohort and nested case-control study in the UK. *Drug Safety* 2005; **28:** 241–9.
6. Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2005; **365:** 1543–51.
7. Archer DF, *et al.* Endometrial effects of tibolone. *J Clin Endocrinol Metab* 2007; **92:** 911–18.

Effects on the cardiovascular system. A study[1,2] of tibolone in the treatment of osteoporosis in postmenopausal women found that although it reduced the risk of fracture there was an increased risk of stroke.

1. Grobbee DE. LIFT study to continue as planned. *BMJ* 2005; **331:** 843.
2. Cummings SR. LIFT study is discontinued. *BMJ* 2006; **332:** 667.

Precautions

Tibolone is contra-indicated in women with hormone-dependent tumours, cardiovascular or cerebrovascular disorders including thrombophlebitis, thromboembolic processes, or a history of these conditions, undiagnosed vaginal bleeding, untreated endometrial hyperplasia, porphyria, and severe liver disorders. It should not be given to pregnant women and is not intended for use in premenopausal women, except those being treated with a gonadorelin analogue. Use of tibolone within 12 months of a natural menopause is also not recommended because irregular vaginal bleeding is likely. In postmenopausal women, vaginal bleeding starting after 3 months or more of treatment, or recurrent or persistent bleeding, should be investigated.

Care should be taken when giving tibolone to patients with uterine fibroids, endometriosis, liver disease, disorders that may be exacerbated by fluid retention such as cardiac or renal dysfunction, hypertension, epilepsy, or migraine, or with a history of these conditions. It should also be given with caution to patients with dyslipidaemia or diabetes mellitus. Tibolone should be stopped if there are signs of thromboembolism, a significant increase in blood pressure, new onset of migraine-type headache, or if abnormal liver function tests or cholestatic jaundice occur. Consideration should be given to stopping tibolone 4 to 6 weeks before elective surgery when prolonged immobilisation after surgery is likely.

Malignant neoplasms. Licensed product information for tibolone advises that it is contra-indicated in women with a history of hormone-dependent tumours. However, the risk of cancer recurrence associated with tibolone has not been determined and there have been a few reports of its use for menopausal symptoms in such patients. An observational study[1] and a case-control study[2] of women who had been treated for breast cancer found no evidence that tumour recurrence was higher in those subsequently given tibolone than in those who were not. Case-control studies have also suggested that tibolone does not increase the risk of recurrence of treated endometrial[3] or ovarian[4] cancers. Although promising, these data are limited and further studies are needed to confirm the safety of tibolone in these groups of patients, particularly as there is some evidence[5] that in UK general practice it may have been prescribed preferentially to women at increased risk of breast and endometrial cancers, including women with a history of breast cancer.

For reports of the incidence of breast and endometrial cancers in women given tibolone, see Carcinogenicity, above.

1. Dimitrakakis C, *et al.* Clinical effects of tibolone in postmenopausal women after 5 years of tamoxifen therapy for breast cancer. *Climacteric* 2005; **8:** 342–51.
2. Goutzioulis M, *et al.* Tibolone therapy in breast cancer survivors: a retrospective study. *J Obstet Gynaecol Res* 2007; **33:** 68–73.
3. Lee K-B, *et al.* Endometrial cancer patients and tibolone: a matched case-control study. *Maturitas* 2006; **55:** 264–9.
4. Lee K-B, *et al.* The safety of tibolone in epithelial ovarian cancer patients. *Maturitas* 2006; **55:** 156–61.
5. Velthuis-te Wierik EJM, *et al.* Preferential prescribing of tibolone and combined estrogen plus progestogen therapy in postmenopausal women. *Menopause* 2007; **14:** 518–27.

Interactions

Compounds that induce liver enzymes, such as phenytoin, carbamazepine, and rifampicin, might theoretically enhance the metabolism of tibolone and thus reduce its activity.

For reference to the effect of tibolone on the activity of oral anticoagulants, see Sex Hormones under Warfarin, p.1431.

Pharmacokinetics

Tibolone is rapidly and extensively absorbed after oral doses and quickly metabolised into three active metabolites, two of which have mainly oestrogenic activity while the third, like the parent compound, has progestogenic and androgenic activity. Peak concentrations of tibolone and its metabolites occur after about 1 to 1.5 hours, and the two main metabolites have an elimination half-life of about 7 hours. Metabolites are excreted in the bile and eliminated in the faeces. About 30% of a dose is excreted in the urine.

◊ References.

1. Timmer CJ, Doorstam DP. Effect of renal impairment on the pharmacokinetics of a single oral dose of tibolone 2.5 mg in early postmenopausal women. *Pharmacotherapy* 2002; **22:** 148–53.
2. Timmer CJ, Huisman JA. Effect of a standardized meal on the bioavailability of a single oral dose of tibolone 2.5 mg in healthy postmenopausal women. *Pharmacotherapy* 2002; **22:** 310–15.
3. Timmer CJ, *et al.* Pharmacokinetics of tibolone in early and late postmenopausal women. *Br J Clin Pharmacol* 2002; **54:** 101–6.
4. Verheul HAM, *et al.* Pharmacokinetic parameters of sulfated tibolone metabolites in postmenopausal women after single and multiple doses of tibolone. *Clin Pharmacol Ther* 2007; **81:** 573–9.